VIRGINIA INHALATION TOXICOLOGY ADVISORY GROUP

MINUTES-UNAPPROVED DRAFT

THIRD MEETING
APRIL 9, 2009

TIME AND PLACE: 9:00AM – 4:00 PM
DEQ Central Office
629 E. Main Street
Richmond, VA 22469
Conference Room A

PRESIDING: Patricia McMurray, DEQ Risk Assessor Program Manager

MEMBERS PRESENT:

Jim Gould, Sierra Club
John Morris, Ph.D., University of Connecticut (SOT)
Debbie Mulrooney, DuPont (VMA) – by phone
(also Dave Kelly, DuPont Inhalation Toxicologist – by phone)
Kevin Wallace, M. D., University of Virginia
Kimber White, Ph. D., Virginia Commonwealth University
Dwight Flammia, Ph.D., Virginia Department of Health

DEQ STAFF PRESENT:

Patty Buonviri, Air Toxics Coordinator (Recorder)
Alan Anthony, Ph.D., Risk Assessor, Air Toxics (Timekeeper)
Michael Dowd, Air Director

AT&T Connect was used to link those by telephone to presentations.

VINTAG members and DEQ staff introduced themselves.

The meeting minutes from the second meeting were approved with one change. On the last page the minutes should have stated that there are four compounds that would need to be evaluated instead of two if a 10 times factor for carcinogens is used. DEQ staff will make the change and the final minutes will be posted on the Virginia Town Hall within three days of approval. See http://www.townhall.state.va.us/L/meetings.cfm for the minutes from the last meeting.

The status of action items from the previous meeting was reviewed.

ACTION: DEQ will provide support documents and critical study papers.

Members can now access support documents and critical study papers on the DEQ website at http://www.deq.virginia.gov/air/toxics_workgroup/Toxics_Work_Group.html. All members present except one was able to access the information.

ACTION: DEQ will distribute draft criteria and coordinate comments. One member drafted a list of study criteria to be considered for each assigned chemical review. DEQ distributed the draft list of study criteria to consider for the assigned chemicals.

ACTION: DEQ will look into whether New Jersey has a documented rationale for choosing their numbers. DEQ talked to New Jersey and found that they review their numbers every two years, they do not necessarily use the most conservative value, and preference is given to IRIS values. They are due to be updated this year. DEQ also talked to Maryland and found they use the California EPA number, have no formal process and the numbers are due to be updated this year.

DEQ mentioned that staff had met with management to discuss the options for evaluating cancer**.** A decision was made not to provide suggestions to the VINTAG group – that VINTAG is encouraged to make their recommendations and DEQ management will then consider the recommendations in determining a course of action.

An outline for review was sent to members so the review would be consistent. The following are summaries of member's chemical specific review for chronic non-cancer inhalation toxicity.

Acetaldehyde: The US EPA's (EPA) review was over 10 years ago while California EPA's (Cal EPA) review was six months ago. Both EPA and Cal EPA's review used the same inhalation critical study. The member noted that acetaldehyde is normally present in the human body. The main difference was what was done after the point of departure. EPA uses a 15 year old approach that is not supported by data – assumes human levels 7 times higher than in rodents. EPA's toxicity value is nine ug/m^3 which is less than what humans typically exhale. Cal EPA used an uncertainty factor of 300 rather than 1000 and ended up with a HEC of 43 mg/m^3. The main reasons for the difference are that Cal EPA used inhalation dosimetry and a benchmark concentration rather then a NOAEL. In summary, CaL EPA uses more recent guidance, uses benchmark concentration, and the dosimetry is more appropriate. On the other hand, EPA's number was 50 fold lower which is less than the concentration of exhaled air. The group consensus was that Cal EPA is more appropriate. Even though they both use the same data set, Cal EPA has a more modern approach for evaluating the data.

Acrolein: Cal EPA had the most recent review. Cal EPA's toxicity value was based on a newer study with a NOAEL rather than just a LOAEL. EPA used a study from the 1970's. The study had a LOAEL but not a NOAEL. EPA used a dosimetry adjustment of 7. EPA used an uncertainty factor of 1000. However, a more recent study show's that's the wrong way to go. Cal EPA used a more recent study with no effect and a total uncertainty factor of 200. Although the Cal EPA toxicity value is more permissive, it is

consistent with the current state of the art. The group consensus is to use the Cal EPA toxicity number.

Carbon Tetrachloride: EPA's review was conducted in 2005 while Cal EPA's review was in 2000. EPA used a 1998 study on rats, while Cal EPA used a 1952 study on guinea pigs. Both studies looked at similar critical effects. The biggest difference in the studies was the uncertainty factors. Cal EPA's study used a LOAEL and not a NOAEL. Cal EPA didn't say why they didn't use the 1998 study even though it was of a longer duration and had a NOAEL. It is possible that Cal EPA may have not had the 1998 study available when they started their review. The member noted that carbon tetrachloride is also a carcinogen. EPA's number is based on an ATSDR Minimal Risk Level (MRL). Because EPA's review was more recent and the study they used was a newer study of a longer duration and had a NOAEL, the group reached consensus to use the EPA number.

Ethylene dichloride: Member absent, review postponed.

Adjourn for break.

Mercury: (elemental form of mercury (HG^0)) EPA has a chronic non-cancer inhalation toxicity of 0.3 micrograms/m^3 (1995) while Cal EPA's value is 0.03 microgr/m3 (2008). The point of departure and the data set is the same for both agencies. A LOAEL bracketed POD was chosen. The member stated that there were limitations to the data set. The exposure was based on extrapolation from blood levels and not actual air. The strength of the studies is that it was a human study with neurological effects. The limitations of the design include test validity, exposed group size, dose-response gradient, and effect sensitivity and were confounded by alcohol consumption, sleep cycle disturbance, and medications. Four of the studies came up with about the same answer. Other studies showed no significant difference in psychological performance or in cardiovascular reflexes. The POD (LOAEL) adjusted for continuous exposure was 9 ug/m3. Uncertainty factors included LOAEL/NOAEL, subchronic/chronic, interspecies, and intraspecies. EPA's uncertainty factor was 30 while Cal EPA's was 300. Cal EPA has extra intraspecies uncertainty to account for neurodevelopmental effects. The ASTDR plot of significant exposure for inhalation points out an additional study in which squirrel monkeys were exposed in utero. When the LOAEL is adjusted to continuous exposure, the POD is 60 ug/m^3. If standard uncertainty factors were applied, the exposure limit based on this study would be 2 ug/m^3. This value is closer to the U. S. EPA RfC than the Cal EPA REL. There is more support for using the EPA number but additional review is needed. Since the monkey study addresses developmental exposure, it accounts for the uncertainty factor used by CalEPA. In addition, there were limitations associated with the human studies.

Although the group agreed with the reviewer's assessment, some thought that more review may be needed. DEQ stated that we don't have to reach consensus here if the group doesn't like the strength of the data set and feels that neither is right. There is also concern about the validity of measures. One member suggested giving it to VDH to review.

The presentation will be posted on DEQ web site.

DEQ suggested checking with Roy Smith, an EPA toxicologist. We could show him the study and see what he says. Cal EPA number was done recently, why did they chose their number? One member said that mercury can form a vapor that can be inhaled. There have been case reports of individual that have been affected. The current DEQ SAAC is 0.02 micrograms/m^3. (Note that this is for the alkyl forms.) This seems to be risk conservative.

Tetrachloroethylene (PCE)

PCE is a probable but not an established carcinogen. EPA has a proposed toxicity value of 20 ug/m^3 and Cal EPA's current value is 35 micrograms/m^3. EPA's current number is 270 ug/m^3 and is based on an ATSDR MRL. The main source of PCE is from dry cleaning operations although it is also used in some chemical manufacturing processes and it is also an effective solvent. There are no referenced studies for Cal EPA. EPA cites a study by Altmann in 1995 that used dry clean shop neighbors as the exposed group. The ATSDR number is based on a study by Ferroni in 1992 using female dry clean shop workers. The critical effect in both studies was neurobehavioral dysfunction. The LOAEL in the EPA study was lower (4.8 mg/m^3) than that in the ATSDR (102 mg/$m^{3)}$

Strengths of the studies include relevance to human exposure and health effects of concern. However these studies had similar limitations to those from the mercury study such as no dose-response gradient, effect sensitivity, and confounding factors such as alcohol consumption, sleep cycle disturbance and medication use. Altmann had 14 participants and used passive indoor air sampling while Ferroni had a sample size of 60 and the air test method is unknown.

There was some concern whether this was a valid data set and about intergender uncertainty. In Connecticut, cancer risk projections drive the number. Michigan also uses cancer. If PCE is both a carcinogen and a non carcinogen, DEQ will still need to consider the non carcinogenic number. The uncertainty factor for the EPA study was 300, and was 100 for the ATSDR study. California did not document their uncertainty factor.

There was concern that the EPA study doesn't hold up and that there is a loose association at best.

This chemical will stay on table. DEQ will contact Cal EPA to see where they got their number. Which number is more scientifically defensible? Why suggest interim numbers? DEQ could be challenged if there is no basis for their number. EPA is currently using the ASTDR number of 270. The group recommended using the current EPA number as it appears to be the most documented. However, further review is needed to see what's going on. If the group had to make a decision, they are leaning

towards the ATSDR (current EPA number). EPA's number is more restrictive than the current SAAC (678 ug/m^3). The group reached a consensus to go with the current EPA number, pending additional review from DEQ on information from Cal EPA (what study did they use) and on the proposed EPA number. If the proposed EPA number gets approved (the group thinks the study is bad) then what do we do? The group could pick the Cal EPA number over the EPA number.

The presentation will be posted on DEQ web site.

Toluene: EPA's current value is 5.00 x 10^3 and was derived from human occupational studies during the time period of 1995 to 2001. The study exposed people to toluene followed by a dose response study resulting in neurological effects and loss of color sensitivity (loss in recognition of shade differentiation). EPA's review came out in 2005 and is the most recent review. Cal EPA's toxicity level is lower at 3.00 x 10^2 and cites a 1995 rat study. Cal EPA used a rat study over a human study because the rat study had a more sensitive endpoint. As a result Cal EPA had a higher uncertainty factor (100) resulting in the lower number while EPA used an uncertainty factor of 10 because the study involved humans. Members questioned Cal EPA's use of a lower number using an animal study over EPA's higher number using a human study. Cal EPA has reduced emission allowances based on a nonhuman studies done in 1995. Because EPA used more recent human studies, the EPA number seems to have a stronger basis. If you take out the uncertainty factor, then the numbers are very close. The study shows the NOAELs are the same and that the uncertainty factor used in Cal EPA is not necessary. Data sets seem concurrent with equal sensitivity which members thought was another reason to take the EPA number. Since the number changes only because of the uncertainty factor used, the group is more inclined to go with the human number. The group reached consensus to recommend the EPA number.

Triethylamine: Member absent, review postponed

Xylenes: EPA had the most recent review and has a lower number. EPA used a rat study that had a NOAEL. The study included a motor coordination test and they also measured serum chemistry values. The group thought it is better to use brain concentration rather than serum. EPA used an uncertainty factor of 300 which resulted in a toxicity value of 100 ug/m^3

Cal EPA was not able to find data that had a NOAEL only a LOAEL. The study Cal EPA used was a human occupational study lasting 7 years involving Chinese factory workers. The test group consisted of 175 workers and there were 241 in the control group. Cal EPA's toxicity value is 700 ug/m^3. It was noted that the workers were also exposed to other solvents as well xylenes. Also the workers completed the survey which creates a subjective bias. The study showed significant differences between workers and control group. However there were no differences in serum levels. Cal EPA applied an uncertainty factor of 30.

The group agreed that a single human study is problematic. The member stated that Cal EPA did not even mention the study that EPA used. Also it's possible the critical effect for neurobehavioral dysfunction might be below that of irritant. Also it was suggested that the background level in China would not be the same as it is in the United States. One member said that it would have been nice if blood levels had been checked. All other factors from both groups were about the same based on responses to the questionnaire. A member mentioned that pain sensitivity is known to increase with exposure (threshold for pain). The group reached a consensus to go with the EPA number which is more risk conservative.

A member remarked that EPA picked a rat study over a human study because they had concerns with the human study such as self-reporting, lack of reporting of exposure duration, and that there was no clear dose-response.

Summary:
The group reached consensus on acetaldehyde, acrolein, carbon tetrachloride, toluene, and xylene. For tetrachloroethylene, the group is leaning toward the current EPA number but would like more time to review before reaching a decision. Ethylene dichloride and triethylamine reviews were postponed because the members assigned were not present.

The group did not reach a consensus on mercury and decided further evaluation was needed before a decision could be reached.

DEQ reviewed the decision tree to see if the group was comfortable with the added preferences. The following recommendations were made for DEQ to follow when evaluating studies without guidance from VINTAG. Multiple scientifically sound human studies should take precedence. Also preference should be given to studies that demonstrate dose response and include both a LOAEL and a NOAEL. The most recent review should not necessarily be the sole basis for decision. BMC is preferable over NOAEL.

DEQ plans to perform periodic reviews internally. For periodic reviews DEQ and VDH may be able to review and come to consensus. DEQ would probably want outside experts if DEQ and VDH did not reach consensus.

DEQ expressed appreciation for all the work done by members in preparing their reviews.

Adjourn for lunch

Inhalation Unit Risk Approach

What should DEQ use as we go forward? DEQ needs to establish a method to choose toxicity values as chemicals are updated.

Tentative Decision Tree to Determine Chronic Inhalation Reference Values- Periodic Review

How often should a review be conducted? For future reviews, DEQ and Virginia Department of Health (VDH) staff would be used to review and arrive at a consensus. If a consensus can not be reached, then DEQ would try to reconvene VINTAG acknowledging that the group may not be the current members. The group gave consensus for this proposed process.

A suggestion was made that the review should be conducted once every 4 years, although some states do reviews every two years. One member advocated allowing more time between reviews rather than not having enough time and the review fall behind schedule. Also the longer time between reviews allows time for more science to be generated. It was agreed that the review should normally be conducted every four years, but DEQ could expedite a review based on significant health impact. DEQ questioned whether a memorandum of understanding (MOU) would be needed between DEQ and VDH for the review process. VDH will check.

ACTION: VDH

DEQ began the discussion on chronic cancer toxicity values. DEQ presented a possible decision process for selecting chronic cancer toxicity factors. DEQ summarized what guidance is available. DEQ noted that the latest guidance for carcinogen risk assessment was published in 2005 by U. S. EPA. One member questioned whether or not the guidelines have been implemented. The guidelines emphasize using a mode of action when it is known rather than a default linear extrapolation. Adjustments are made for early life susceptibility for chemicals with a mutagenic mode of action. A question was posed how would you incorporate into toxicity factors for the mutagenic portion? This would mainly be a concern for PAHs and vinyl chloride.

Cal EPA's guidance came out in 2005 for their Air Toxics Hot Spots program. Their guidance refers back to EPA's 1986 guidelines. It was noted that most of the Cal EPA numbers are based on 1986 guidelines. Cal EPA didn't derive new numbers in 2005, only reviewed the existing numbers.

In decision tree, there are two options: one is to compare Cal EPA and EPA's numbers. For cancer, the group decided that numbers differing by up to ten times is more reasonable as the numbers are essentially the same. The group discussed using the most conservative or the most recent review if the values differed by ten times or less. If the values differ by more than ten times, then the VINTAG group would do the review. However, the group voiced concern that they did not have the expertise for conducting cancer reviews. Alternatively, a suggestion was made that for values differing by less than ten times, the more recent number could be used and if the value differs by more than ten times use the most conservative number. Based on this approach, only four chemicals would need to be reviewed by VINTAG. They are arsenic, epicholorhydrin, formaldehyde and 2-nitropropane.

The formaldehyde number would likely affect the most facilities. One facility is known to use epicholorhydrin. The group remarked that they may be able to come up with a number but that they don't really have the expertise. A quick review of each chemical was provided.

Arsenic EPA toxicity value is 4.3×10^{-3} and is an absolute risk. Cal EPA's number is 3.3×10^{-4} and is a relative risk that is adjusted for smoking. A member said he didn't have the expertise to know whether absolute or relative risk should be used.

It was suggested that you could go with more conservative value since there is more than a 10 fold difference between EPA's and Cal EPA's numbers. Arsenic is epigenetic so both values may be wrong. Arsenic may also affect DNA methylation. It was noted that the use of models may not be appropriate. A suggestion was made to use the more conservative number and if someone doesn't like it they can petition to have the number changed. Another member made the argument that you could also take the EPA number because the science is more recent.

Epichlorohydrin: Epichlorohydrin is listed as a 2A probable carcinogen (2 means human data is inadequate). EPA's toxicity value is 0.12×10^{-5}. EPA's policy on site of contact states the need to use the right route.

Cal EPA's value is 2.3×10^{-5} and as is based on a rat drinking water study. One member questioned why look at water as it's not a good way to predict inhalation risk. There were no problems with the lung identified in the study. When the epichlorohydrin hits the nose it causes cancer there and when it hits the stomach it causes cancer there. The member notes there was also a subcutaneous injection study that produced a local sarcoma.

An inhalation study is more relevant to assessing risk. Cal EPA had a problem with this study because of early mortality. With early mortality there is a decrease in cancer incidence because the sensitive population is removed. Maybe neither study is good. Perhaps you can infer what Cal EPA determined that the risk may be underestimated because of early mortality. So instead they used the results from the drinking water study to guesstimate what the risk might be. Cal EPA took papilloma data and calculated unit risk and compared it to the amount of air breathed to scale up the number from the drinking study. It was agreed that neither study is very good. EPA says the drinking water study was terminated at 81 weeks and overestimated the concentration because of short shelf life. Each criticizes the other's study.

The group agreed to put the discussion on hold.

Formaldehyde: EPA's current value is 1.3×10^{-5} and Cal EPA's number is 6.6×10^{-6}

Both EPA and Cal EPA used a 1988 study and both used modeling although there was no accepted model for formaldehyde in 1988.

The number used by the EPA Office of Air Toxics ($5.5 \times 10^{-9)}$ is a value developed by the Chemical Industry Institute of Toxicology (CIIT) based on a fluid dynamic/two stage clonal growth model. There are a few papers that address the uncertainties in the clonal growth model but they don't seem to make that much difference. There are two parts to the model- the dosimetry model to get the flux from rat to human and clonal growth model, showing tumors caused by increasing cell proliferation. The mode of action is cell proliferation and not mutations. At high concentrations the cancer dose response is non linear. National Center for Environmental Assessment (NCEA) has not embraced the low OAQPS number. External peer review is scheduled to be conducted in FY 2010.

One member suggested that a decision to use the EPA number of 5.5×10^{-9} should not be used without a review by an expert panel.

IRIS's evaluation should be finalized in 2011 and will be based on a human leukemia study. Cal EPA's noncarcinogenic number is 9 ug/m^3. By old unit risks, 9 is a risk of 1 in 10,000 (EPA) or 6 in 100,000 (CalEPA). If the CIIT unit risk is used, the noncancer number would be more restrictive based on asthma exacerbation in children. Depending on the model used, risk varies by 3 orders of magnitude.

2- nitropropane: EPA's OAQPS's value is 5.6×10^{-6} ug/m^3. This number comes from a Dutch expert committee on occupational standards adjusted for lifetime exposure. New Jersey's number is 2.7×10^{-3} ug/m^3.

2-nitorpopane is not a byproduct of combustion (based on AP-42), has no reactive bonds and is used primarily as a solvent, in explosives, and in racing cars. The compound is a liver carcinogen in mice. There may not be any source in Virginia that uses this chemical.

There is currently no IRIS or CalEPA unit risk for 2-nitropropane.

The group doesn't feel they have expertise to make decision on these chemicals. A recommendation was made to take the most conservative value (from decision tree) with the option for people to petition DEQ for a health evaluation.

In summary, the group took a look at four carcinogens and came to the conclusion that they didn't have the expertise and the lack of information prevented the group from making a decision based on science. The group thought that an informed decision would take a more thorough review by an expert group and perhaps more studies. DEQ is concerned about bias. It is possible that another person could provide a risk assessment to document another number. DEQ would need to review the document to see if it supported the claims. VINTAG members may be able to provide cancer expertise from SOT or from the group's respective university to help DEQ make a decision.

Part of the member's discomfort in recommending a value is that they don't have the documents to review. Another consideration is that 3 of 4 chemicals are some of the

most controversial. The members thought it would be difficult to make an informed decision. DEQ may want to make a policy decision to take the EPA number. Where there's more than one EPA number, which number should be used? It was suggested that the EPA IRIS number be used. The public has the right to petition DEQ to have the number reviewed.

DEQ gave a recap of the decisions that were made. Go with the EPA IRIS number first because Virginia doesn't have expertise. If EPA has established guidelines more recently, then Virginia should rely on the state of the science. Part of DEQ's four year review should include a look at who is using the best methodology.

The group consensus was that preference should be given to the EPA IRIS values because EPA uses newer scientific approaches. DEQ will do a review every four years unless petitioned by the public. Public petitions should be developed during the ad hoc process. The basis for a petition can be written into the regulation. The information required should include a scientifically sound risk assessment.

DEQ and the VDH would perform the review and if a consensus is not reached, the VINTAG would be reconvened which could include current members, new members or coworkers of current members.

What is an acceptable risk? 1 in 1,000,000 or 1 in 10,000? This will be a DEQ management decision.

In the end, the group decided to defer on 2-nitropropane and for the other 3 carcinogens to go with the current EPA IRIS number.

Adjourn for break

For the next meeting, there are two more noncancer evaluations to go over and we should continue review of mercury.

VINTAG Action Item: Review the presentation on mercury and be prepared to discuss further.

DEQ Action Item: For PCE, DEQ will try to identify how Cal EPA derived their number.

DEQ Action Item: Write a draft of what we need for the petition process including the minimum requirements.

Next meeting we will start discussing acute values. DEQ has gathered a lot of information from 3 or 4 organizations that have values. EPA has some Acute Exposure Guideline Levels (AEGL) (some are emergencies) and the National Academy of Science has a book on procedures for developing acute exposure guideline levels for hazardous chemicals. Cal EPA also has published some acute numbers and so has New Jersey.

Some compounds have Emergency Response Planning Guidelines (ERPG) and some have a temporary emergency exposure limit (TEEL). However DEQ doesn't have backup documents for those (DOE).

One member stated that non emergency standards are usually a higher number than long term numbers. There is one number for long term exposure and one for hourly and/or 24 hour exposure.

There was some confusion about what time frame DEQ wanted. The current SAAC has an annual and an hourly number. The group can decide what time frame should be used. Also the terms need to be clearly defined to help establish what the numbers should be. Non cancer endpoints should be used for short term limits. Members can provide an ERPG, if needed. DEQ has chemical profiles for ERPGs and AEGLs but need the TEELs from DOE. A member volunteered to look for chemical profiles for the TEELs for the HAPs.

Because emergency values allow for injury, this shouldn't be the basis for the DEQ numbers. The goal is to prevent injury. These numbers may not be relevant. Cal EPA may use the numbers and then adjust them.

One member wondered whether the group should be deciding the numbers or just the approach to be used. DEQ noted that existing SAACs have chronic and short term numbers.

One member asked how the emissions were currently monitored. DEQ monitoring values are based on a 24 hour sample. One member said that a short acting irritant would be derived by dividing the peak concentration by 3. From a toxicological aspect, the value should be an 8 hour number. It was noted that Cal EPA has some 8 hour values and a few that are one hour.

DEQ thought that this may take two meetings. The first would be to develop a framework. DEQ needs to define our goals and what databases or other information we have available. Then DEQ can get advice on where to go from there. At the next meeting DEQ will provide information and the following meeting will seek advice from the group.

DEQ would like a complete list but is more concerned about the quality of the values chosen so some decisions may have to be reserved until better data is available. One member said that Michigan has short term numbers but it is unclear how the numbers were derived. DEQ requested the member to try to get Michigan's methodology in writing. Another member said that ATSDR also has short term numbers (less than or equal to a week).

The next meeting was scheduled for May 21, 2009 at 9:00 a.m.

Comments:

One member requested that if anyone uses abbreviations to please spell it out for those that aren't familiar with it.

Meeting adjourned at 3:10 p.m.